LATEST NEWS REGARDING THE MOLECULAR MUTATION PROJECT OF THE IWG-PM

IWG-PM/MOLECULAR PROJECT

The Molecular Project of the International Working Group for Prognosis in MDS (IWG-PM) has been working to develop a clinical-molecular risk model (IPSS-Molecular or IPSS-M). To this end, mutations in diagnostic MDS samples from 2957 patients from 13 countries and 25 global centers were analyzed. These data were presented by Elli Papaemmanuil and Elsa Bernard at the Toronto MDS Symposium and the IWG-PM group meeting, and submitted as an abstract to the 2021 American Society of Hematology meeting. Clinical, cytogenetic, and molecular variables were evaluated for associations with leukemic transformation and overall survival. At least one genetic driver alteration in 94% of patients. Multivariate analysis identified multi-hit TP53, FLT3 mutation, and MLL partial tandem duplication as top genetic predictors of adverse outcomes. SF3B1 mutation was associated with favorable outcomes, but this was modulated by co-mutation patterns. Using hematologic, cytogenetic and molecular data on 31 genes, the IPSS-M was developed as a continuous score. A discrete six-category risk schema was further derived. The IPSS-M re-stratified 46% of MDS patients compared to the IPSS-R, improving discrimination across clinical endpoints. A web calculator was built that, upon entering predictor variables, outputs a patient-tailored score, its corresponding risk category, and temporal estimates for clinical endpoints. The IPSS-M prognostic risk score is personalized, interpretable and reproducible. Combining conventional parameters with genomic profiling, the IPSS-M represents a valuable tool for clinical decision-making for MDS patients.

Other ongoing aims for the Molecular Project include generating data for an MDS classification model, genetic predictors of response to HMAs, and analysis of mechanisms of disease progression obtained from sequential profiling.

At the Toronto IWG-PM group meeting, updates were also provided by Andrea Pellagatti regarding his project, Gene expression in MDS HSPCs using single cell analysis: Disease pathophysiology and outcome prediction, and by Andrea Kuendgen regarding cytogenic features from the treatment-related MDS project.

Also reviewed were publications related to recent efforts by members of the group:

4. Papaemmanuil E, Classification and personalized prognosis in MDS. MDS Foundation Symposium, ASH meeting, 2019 Orlando, December.

This global project is being coordinated by Ben Ebert and Peter Greenberg (co-Chairs), Rafael Bejar and Ellie Papaemmanuil, with statistical support by Donna Neuberg, Kristin Stevenson and Heinz Tuechler.